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09/294,980	04/19/1999	J. OLIVER DOLLY	17259(AP)	6681

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EXAMINER	
BAKER, ANNE MARIE	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/294,980	Applicant(s) DOLLY ET AL.
	Examiner Anne Baker	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[X] Responsive to communication(s) filed on *29 January 2002* .

2a)[X] This action is **FINAL**. 2b)[ ] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[X] Claim(s) *1-6,9,11 and 13-24* is/are pending in the application.

4a) Of the above claim(s) *11,13-1517-24* is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[X] Claim(s) *1-6,9 and 16* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [X] Other: *detailed action* .

DETAILED ACTION

The amendment filed January 29, 2002 (Paper No. 17) has been entered. Claim 1 has been amended.

Claims 1-6, 9, 11, and 13-24 are pending in the instant application.

Claims 11, 13-15, and 17-24 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Paper No. 15.

This application contains claims 11, 13-15, and 17-24 drawn to an invention nonelected with traverse in Paper No. 15. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-6 and 9 encompass non-elected subject matter. The elected invention is limited to preventing expression of a ciliary neurotrophic factor (CNTF) gene. Thus, Claims 1-6 and 9 are examined herein only to the extent that they encompass the elected subject matter.

Claims 1-6, 9, and 16 are examined herein.

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9, and 16 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 4-5 of the Office Action of Paper No. 16 (mailed 7/19/01), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the full scope of the claimed invention. Applicants are referred to the final guidelines on written description (hereinafter referred to as the 'Written Description Guidelines') published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

At page 2, paragraph 4 of the response, Applicants assert that the amendment to Claim 1 to add a functional clause whereby application of the method results in the inhibition of neural sprouting sufficiently narrows the scope of the claim so that the written description requirement is met. Applicants argue that the rejection is not that the inhibition of neural sprouting is not adequately described, but rather that CNTF-inhibiting moieties are not adequately described, and therefore the Examiner is rejecting the original claim rather than the amended claim having the functional clause. First, it is noted that the rejection is clearly being applied to the claims as amended. The amendment to Claim 1 was acknowledged in the first paragraph at page 2 of the Office Action of Paper No. 16 (mailed 7/19/01), where the written description rejection was originally set forth. Second, the lack of the appropriate materials for carrying out the claimed invention is properly a written description issue. The Written Description Guidelines explicitly state that "the issue of a lack of adequate written description may arise even for an original claim when **an aspect** of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention" (paragraph 2 at page 1105). At the time of filing, Applicants were not in possession of the required starting materials for practicing the claimed method. Claim 1 now recites "a composition comprising an agent able to prevent the expression of ... ciliary neurotrophic factor." However, at the time of filing, Applicants were not in possession of such a composition and the specification does not

place the public in possession of such a composition. The specification does not disclose any agent that can be used in the claimed method. In the absence of a written description of the inhibitory agent, the claimed method lacks adequate written description because the inhibitory agent is an essential element of the claimed method. The specification does not disclose the nucleotide sequence of any ribozyme or antisense molecule that can be used to inhibit the expression of a CNTF gene, nor does the specification disclose any other agent that can be used to inhibit the expression of a CNTF gene. In Example 3, the specification discusses the use of a ribozyme directed to neural agrin mRNA, but the nucleotide sequence of this ribozyme is not disclosed. In the instant case, only general teachings are provided for the development of antisense and ribozyme molecules. While the skilled artisan may develop a wide variety of molecules using these general guidelines, there is insufficient guidance regarding which molecules will function *in vivo* in the manner intended. The claim limitations require that the inhibitory agent function to (i) prevent expression of CNTF, (ii) extend the effective period during which tissue treated with clostridial toxin is paralyzed, and (iii) inhibit neural sprouting in the treated tissue.

At page 2, paragraph 5 of the response, Applicants argue that the specification does describe an inhibitory agent capable of inhibiting expression of CNTF because the specification incorporates by reference various teachings relating to the design of ribozymes. Applicants point to Usman et al. (1996), particularly Figures 2 and 4. Applicants further point to the nucleotide sequence of CNTF cDNA. Applicants assert that what is well-known to one of skill in the art need not be described. However, Usman et al. provides only general teachings relating to the development and design of ribozymes. Usman does not provide any specific teachings relating to a ribozyme that would prevent expression of a CNTF. Further, a teaching of a nucleotide sequence for a CNTF cDNA is not sufficient to provide a written description of an inhibitory agent such as a ribozyme or antisense nucleic acid molecule. Neither the specification nor the prior art even points to a **target sequence** within the CNTF cDNA that would be an appropriate target for the ribozyme or antisense molecule. It is further noted that the claims encompass

inhibiting CNTF expression in a wide variety of animals, and therefore have a very broad scope with regard to the various CNTF nucleic acid sequences that would be the target of the inhibitory agent.

At page 2, paragraph 6 of the response, Applicants argue that since the Federal Circuit says that "a description of a genus of cDNAs may be achieved by ... recitation of structural features common to members of the genus" and the instant disclosure provides a CNTF substrate sequence and ribozyme sequence requirements, then the disclosure has provided "structural features common to members of the genus." However, as noted above, the claim limitations require much more than this because the inhibitory agent must possess the 3 biological properties recited in the claims. These are all properties that must be present *in vivo*. Further, as noted above, a single CNTF substrate sequence and general teachings for ribozyme design would not provide a written description for the entire genus of inhibitory agents that could be used in the claimed method. The claim encompasses inhibiting CNTF expression in a wide variety of animals, and therefore would require a variety of inhibitory agents to target these various CNTF nucleic acid sequences.

A ribozyme or antisense nucleic acid molecule is a complex chemical compound, and it is well-established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials. See *Oka* 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinquish it. **It is not sufficient to define it solely by its principal biological property**, because an alleged conception having no more specificity than that **is simply a wish to know the identity of any material with that biological property**. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

At page 3, paragraph 2 of the response, Applicants argue that Example 3 of WO95/32738 describes an exemplary delivery system for ribozymes or antisense agents. The Examiner is aware of the

delivery system disclosed in W) 95/32728. To clarify, the instant rejection does not pertain to the delivery system, but only to the ribozymes and antisense agents themselves.

The limited information regarding the contemplated embodiments is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of agents for the inhibition of CNTF gene expression. Thus, it is concluded that the written description requirement is not satisfied for methods of using the genus of agents recited in the claims.

Claims 1-6, 9, and 16 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 5-7 of the Office Action of Paper No. 16 (mailed 7/19/01), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for extending the effective time tissue is paralyzed with a clostridial toxin comprising administering an agent that prevents the expression of a ciliary neurotrophic factor (CNTF) gene. While the claims encompass the use of any agent to inhibit the expression of CNTF genes, the specification only explicitly contemplates the use of antisense and ribozymes. The specification does not provide any teachings for the use of agents other than antisense or ribozymes. Thus, the enablement rejection advanced herein below is directed specifically to the use of antisense and ribozymes, but applies broadly to the use of any agent that will inhibit the expression of a CNTF gene.

At page 3, paragraph 6 of the response, Applicants suggest that Examiner doubts the utility of the claimed invention and therefore the rejection should be advanced under utility rather than enablement. To clarify, the absence of a utility rejection indicates that the Examiner accepts the asserted utility as a credible utility, albeit one that is not enabled by the limited information provided in the instant disclosure.

At page 3, paragraph 7 of the response, Applicants argue that methods of inhibiting CNTF expression which do not result in an inhibition of biological effect are not covered by the claims.

However, the enablement issue is separate from this issue. It is well-established that the claims can properly encompass inoperative embodiments. This is not the issue here; rather the lack of sufficient guidance for finding a single operative embodiment is at issue. Given the unpredictability of ribozyme and antisense design for *in vivo* applications, for reasons of record, the lack of working examples directed to inhibition of CNTF expression, the broad scope of the claims, and the limited guidance in the specification, undue experimentation would have been required to practice the claimed method.

At page 3, paragraph 7 of the response, Applicants again argue that they have provided an example describing a delivery system for the ribozyme or antisense agent. However, the delivery system is not an aspect of the enablement rejection. The enablement rejection is based on the lack of guidance for designing, preparing, and using appropriate inhibitory agents that could be used in the claimed method.

At page 4, paragraph 1 of the response, Applicants argue that the CAFC has said that the specification need not teach, and preferably omits what is well-known in the art. However, agents for inhibiting the expression of CNTF were not well-known in the art. The specification does not describe a single agent that would prevent expression of CNTF either *in vitro* or *in vivo*. When there is no disclosure of any specific starting materials, there is a failure to meet the enablement requirement. The Federal Circuit has clarified this point, stating that the general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.** It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification

only provides a starting point, a direction for further research. *Genentech Inc. v. Novo Nordisk A S*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (CAFC 1997), *cert. denied*, 118 S. Ct. 397 (1997) (emphasis added).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner* et al. 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

At page 4, paragraph 1 of the response, Applicants point to some references cited on page 9 of the specification that provide general teachings for ribozyme and antisense design and assert that the skilled artisan could have used this knowledge in combination with the pitfalls mentioned in Good et al. (1997), as cited by the Examiner, to design the necessary inhibitory agents. However, general teachings are not sufficient to provide the skilled artisan with the necessary guidance for carrying out the claimed invention, as it has already been established that the *in vivo* effects of ribozyme and antisense agents is unpredictable and the instant specification does not offer specific guidance for overcoming the problems acknowledged by those of skill in the art.

The Examiner accepts Applicants explanation that the clostridial toxin can be administered after administration of the inhibitory agent.

A new enablement issue arises in regard to the claim amendments. Claim 1 has been amended to recite new step (b) which involves contacting the tissue with a clostridial toxin. The claim also recites that neural sprouting is inhibited upon treatment with the CNTF inhibitor. However, the specification teaches that the administration of the CNTF inhibitor is intended to enhance the effect of the clostridial toxin, but does not itself inhibit neural sprouting prior to the administration of the clostridial toxin. Thus,

it appears that the wherein clause should be placed after both steps (a) and (b) have been performed, regardless of the order of the steps. The specification does not suggest or contemplate inhibiting neural sprouting solely by administration of a CNTF inhibitor, in the absence of clostridial toxin.

All other aspects of the enablement rejection are maintained, for reasons of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 9, and 16 stand and are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 3 are indefinite in their recitation of "said contacting step" because the phrase has ambiguous antecedent basis. Claim 1 has been amended to add a second contacting step in step (b). Thus, it is unclear to which contacting step Claims 2 and 3 are referring.

Claims 1-6, 9, and 16 are indefinite because the claims encompass non-elected subject matter.

Applicants assert that the amendment to Claim 1 repairs this problem. However, the claims still encompass non-elected subject matter because they recite numerous polypeptides other than CNTF and Claim 6 still recites a variety of other types of inhibitory agents that do not read on the elected subject matter.

Claims 1-6, 9, and 16 are indefinite in their recitation of "neural sprouting" because it is unclear what specific biological activity is being inhibited. At page 10, the specification states:

> First, the poisoned endplate becomes synaptically inactive. Shortly thereafter the endplate elaborates thin nascent axon neural processes. These processes or "sprouts" are synaptically competent after about 14 days following treatment with clostridial neurotoxin. The sprouts continue growing, reaching a maximal length and level of complexity after about 42 days following treatment with neurotoxin. During this time, the endplate remains synaptically inactive.

However, it is unclear whether "sprouting" refers to the point at which the processes initially appear or the continued growth of the sprouts or both. The specification does not define the term "neural sprouting". Thus, the metes and bounds of the claims are not clearly set forth.

Applicants argue that the sentence bridging pages 14 and 15 clarifies this issue, but the cited sentence does not adequately define "neural sprouting." The sentence refers to "one of the major steps of the sprouting phenomenon," but since the metes and bounds of the "sprouting phenomenon" are unclear this sentence does not clarify the meaning of "neural sprouting."

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER